RENAL FUNCTION OF THE RAT DURING EXPERIMENTAL HYPERTENSION

A THESIS

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ABSTRACT OF THESIS

This investigation involved the determination of renal function in rats during a period of experimental hypertension. Rats were rendered hypertensive by partially ligating the left renal artery and removing the right kidney. A unilateral nephrectomy was performed on the experimental rats, and controls (both kidneys present) were used as comparative groups.

Renal function tests consisted of plasma clearance of inulin and phenol red retention determinations. The per cent of body weight of the kidney, heart and adrenal glands were determined.

The results of this work suggested that albino rat kidneys can function during a period of stress so long as a level of systemic exhaustion is not exceeded. The term systemic exhaustion mentioned here has reference to two factors (endocrine and vascular), which elicited a response along with the renin-angiotonin mechanism.

ACKNOWLEDGEMENTS

I wish to thank Dr. George E. Riley and Mr. Luther S. Williams for their invaluable advice and counsel throughout this investigation.

I would like to express also my deepest gratitude and thanks to my wife and children for their patience and understanding.

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CHAPTER I

INTRODUCTION

Many investigators have reported on the role of the kidney in relation to hypertension. Goldblatt (1940) has shown that renal hypertension is directly related to the secretion of an enzyme renin by the kidney.

It is believed that the kidney will secrete renin under normal conditions in order to maintain or control blood pressure. One might ask the question - does stress, created by partial obstruction of the renal artery, cause the kidney to secrete renin in an attempt to continue its control of the blood pressure? Harrow (1943) stated that renin is not effective unless it is injected intravenously, whereas, epinephrine, pituitrin and tyramine all cause a rise in blood pressure, they differ from renin in that the response to an intravenous injection of the latter is not associated with a decrease in peripheral blood flow or fall in skin temperature.

According to the statements by Harrow and others, the kidney, not generally known as an endocrine organ, possesses this endocrine-like function for some specific purpose. This purpose is not clear according to the literature.

A brief discussion of the mechanisms of renal hypertension will follow in order to form a working hypothesis. Goldblatt (1947) stated that

the ischemic kidney liberates into the blood an enzyme, renin, which splits hypertensin I, a polypeptide, from hypertensinogen, an alpha-2 globulin formed by the liver. Hypertensin I has no pressor activity; however, an enzyme present in plasma, "hypertensin-converting enzyme," acts upon hypertensin I to form hypertensin II which is a powerful pressor agent. Tissues in general, kidney, and intestine in particular contain a dipeptidase which destroys hypertensin II. Skeggs, Kahn and Shumway (1956) obtained hypertensin I from horse plasma, which was converted to active hypertensin II by the action of "hypertensin-converting enzyme" from horse plasma.

Hypothetically, the formation of renin by the kidney may not primarily be an attempt by the kidney to maintain blood pressure. It is a "built in" property of this organ to maintain a "critical kidney function level" during disease or stress conditions. Blood pressure elevation then, is a consequence or an adjunct. Damaged kidneys can perform their chief functions (excretion, reabsorption, etc.) remarkably well up to a certain point. If a critical level of kidney function is exceeded renal failure, uremia and death of the animal results. Secretion of renin may be a mechanism which the kidney uses to maintain intrarenal pressure until repair takes place or the alleviation of stress is diminished.

The purpose of this investigation was to study the function of the rat kidneys during a period of stress.

CHAPTER II

REVIEW OF LITERATURE

Smith (1937) stated that all theories of renal function have been based upon the structure of the nephron. He also stated that Ludwig in 1844 suggested that urine formation began with a passive process of filtration of a protein-free fluid in the glomeruli effected by the hydrostatic pressure of the blood. This supposition was strongly supported by the structure of the glomerulus itself and that the membranes to be crossed (the endothelial capillary walls, the basement membrane and the visceral layer of capsular epithelium) were all so thin and lacking in complexity as to argue against specific gravity. Smith continued by stating that in this view the filtrate, essentially identical in composition with plasma except for the absence of protein, must undergo its final elaboration into urine during its passage down the tubules.

Smith considered the above concept of filtration inadequate when the function of the tubules were considered. He reasoned that the tubule in its entire length is supplied by blood that, having been through the capillary tuft of the glomeruli, has lost a great part of its pressure, and it has lost, therefore, the driving force necessary to effect filtration, especially against the osmotic pressure of the plasma proteins.

Due to the cell structure of the tubules, Smith postulated that the possible operations which might be carried out by these tubule cells can be

divided into three categories. (1) They might absorb substances from the fluid in the lumen and return them to the blood; a process which he designated as tubular reabsorption. (2) They might remove substances from the blood and discharge them into the tubular fluid which he designated as tubular excretion. (3) They might manufacture from raw materials, obtained either from the blood or the tubular fluid, new substances which could be discharged either into the tubular fluid; this process he designated as chemical transformation.

Smith discussed theories of other investigators concerning renal function and concluded that it was possible to construct an elaborate theory to explain the formation of urine in terms of filtration plus reabsorption or filtration plus reabsorption plus tubular excretion, without being able to prove its validity at any point. Any two investigators who observed the same evidence, might disagree emphatically about how the evidence should be interpreted.

Twenty-seven years later (1937) to (1964) since the treatise by Smith, much has been learned about the function of the nephron, but still, there is controversy and doubt regarding the function of certain cellular components of the nephron.

Bowman (1842), Cushing (1932), and Richards (1925) have studied the effects of the production of experimental hypertension to gain a better understanding of renal function. Friedman, Sugarman and Selzer (1941) studied the relationship of renal blood pressure and blood flow during experimental hypertension. By constricting the aorta above and below the renal artery aortic orifice, it was found that renal ischemia was not necessary for the initiation or maintenance of a chronic experimental hypertension. Goldblatt

(1940), however, stated that by partially constricting the renal artery of both kidneys in the dog, experimental hypertension would result. Upon removal of the clamps, the condition was alleviated. He stated also that by clamping one renal artery to one kidney and removing the other kidney a chronic hypertensive condition would result.

Drury, et al. (1950) studied the effects of renal hypertension as it was related to a renin substrate. By clamping and releasing the pedicle of the left kidney 5-15 mins., 19 out of 24 rabbits showed cross blanching. He concluded that blanching in the contra-lateral kidney (right) due to the ischemic left kidney may be due to some substance formed by the left kidney and transported to the right. He also concluded that the substance had a non-pressor function.

Gordon and Flasher (1950) studied the effects of a non-pressor substance from ischemic rabbit kidneys which caused renal vasoconstriction. They found that after hepatectomy or abdominal visceration tachyphylaxis to renin was more quickly produced than in the normal rabbit. Their conclusion was that renal hypertension was mediated by the renin-angiotonin mechanism.

Flasher and Drury (1950) investigated the relationship of renin to early renal hypertension in the rabbit. They suggested that angiotonin was more acceptable than hypertensin because the pressor agent was formed when a substance was extracted from normal kidneys (renin) acted on the globulin fraction of the plasma. They stated also that studies did not support the contention that renin is the renal substance concerned in maintaining the elevation of blood pressure in rabbits with early experimental hypertension.

According to the literature stated so far, concerning the production of experimental hypertension, it might be safe to assume that at the onset

of this condition the kidneys must react immediately and make rapid adjustments. Brown and Barker (1962) stated that when an organism was exposed to some factor which places a stress upon the normal homeokinetic balance, it is said to be stressed. They further stated that the organism must adapt itself to resist the stress when it is applied. Brown and Barker also stated that stress in an organism involved three stages: (1) alarm when the animal is first exposed to the shock, (2) adaptation when the organism is able to adjust to the changed environment by the processes under the control of the adrenal cortex, and (3) exhaustion when the animal can no longer maintain its defenses. Brown and Barker stated, however, that the adrenal cortex is made out to be so overwhelmingly important that no other endocrine nor any other physiological system is permitted to play a role.

In the study of experimental renal hypertension, then, it seems that we cannot limit the area of investigation, nor our conclusions, based on one physiological mechanism, but search for a relationship between several functioning systems in order to ascertain a better understanding of the process. Some of the methods and techniques used to study renal function in normaltensive and hypertensive organisms will be reviewed in order to present specific information concerning a very complex process.

Shideman and Rene (1951) attempted to demonstrate the existence of a correlation between the ability of a chemical substance to inhibit succinic dehydrogenase and to suppress the secretion of certain substances by the renal tubules. Data indicated that energy derived from the Kreb's cycle oxidations was specifically designated for certain tubular transport mechanisms. They concluded that some of the energy from the succinate oxidation had an assigned relative specificity in that it was more directly

involved in tubular secretory processes than it was in the mechanisms employed for reabsorption of glucose and phosphate.

Beyer, Painter and Wiebelhaus (1950) investigated the enzymatic factors in renal tubule secretion of phenol red. It was suggested that in order for the tubules to maintain a functional integrity the following principles must be considered:

(1) An anatomic integrity of the tubular cells must not be violated, otherwise, phenol red would not be secreted.

(2) The optimum pH for secretion under these conditions (phenol red secretion) was 7.8.

(3) If oxygen was omitted, no secretion would take place because secretion was an aerobic process.

(4) Compounds which inhibited oxygen uptake inhibited secretion.

(5) Inhibition of oxidases (phenylhydrazine) resulted in a cessation of phenol red secretion.

The authors concluded that oxygen and carbon dioxide were necessary for the overall functional integrity of tubular secretion. Anything that would uncouple oxidation from phosphorylation and the generation of ATP or inhibit transphosphorylation would inhibit many cell functions.

In relation to the enzymatic factors of tubular secretion of phenol red, Grollman (1925) investigated the process in which phenol red combined with protein. He used an adsorption technique of phenol red in hydrophlic systems and determined its adsorption from aqueous solutions by blood charcoal, undissolved casein and gelatin. Grollman concluded that two factors which had an extraordinary effect on the rate of elimination of phenol red independent of renal influence, were the albumin percentage composition and the pH of the albumin.

Inulin, a complex carbohydrate, has been used most extensively in the study of kidney function. Richards, Westfall and Bott (1934) compared the renal excretion of inulin with that of creatinine and xylose. The latter two substances, especially creatinine, have been used quite extensively also to investigate renal excretion.

They administered inulin intravenously, creatinine intraperitoneally and xylose by mouth to unanesthetized dogs and collected urine specimens at varied time intervals, usually 12-52 mins. after each substance was given. Blood from the jugular vein was taken 1 min. before the beginning and 1 min. before the end of each period. It was found that the concentration of inulin in urine was astonishing, as high as 38.5 per cent. Plasma clearance of injected inulin was of the same order as that of injected creatinine and higher than that of xylose. It was suggested that the differences found between inulin and xylose was due to a greater diffusion of xylose than inulin from the renal tubules.

Kaplan and Smith (1935) determined to what extent the rabbit, in respect to renal activity, parallels that of the dog and man. Their results showed that all of the clearances increased with an increase in urine flow and failed to reach a constant value at urine flow rates that were maximal under the conditions of their experiments. Inulin and creatinine clearances were equal.

Masson, Corcoran and Page (1950) investigated the effects of chronic treatment of rats with renin. Unilaterally nephrectomized saline and protein-fed animals were used. It was demonstrated that the rats showed an increased susceptibility to toxic effects of agents such as desoxycorticosterone and anterior pituitary preparations as well as renin. Differences in organ weight and body weight were determined. It was stated that the

toxic effects, diuresis and proteinuria, resulted from the prolonged treatment of renin and that the rapid loss of body weight which was seen in experimental and malignant hypertension may be attributed to a hypersecretion of renin.

Thus, according to the literature which has been reviewed, it seems that several physical, chemical and biological processes are involved in the study of renal function either during a normaltensive state or a hypertensive one.

CHAPTER III

MATERIALS AND METHODS

Twenty-three female albino rats were obtained from the Carolina Biological Supply Company, Burlington, North Carolina. The animals were housed in metal cages; three to a cage. They were weighed and checked periodically to determine their rate of growth and well being. Regular dog chow (Friskies) was used as a basic diet and water was available for the animals ad libitum.

The systolic blood pressure was recorded weekly using a technique described by Friedman and Freed (1952). Briefly, this technique consisted of placing a pneumatic cuff around the tail of the rat which was connected, by polyethylene tubing, to a manometer gauge and suction bulb. Immediately behind the pneumatic cuff was a very sensitive carbon microphone which was connected to a two stage amplifier. The microphone was sensitive enough to detect arterial pulsations when fitted firmly around the rat's tail (Fig. 1).

It was necessary to place the animals in a warm environment (42-45°C for 4 min.) before recording the blood pressures. The warming up process tended to increase blood circulation, hence, aiding the detection of the arterial pulsations (Fig. 2).

The normal range of the systolic blood pressure was determined on all of the stock animals. They were then divided into three groups, A, B and C.

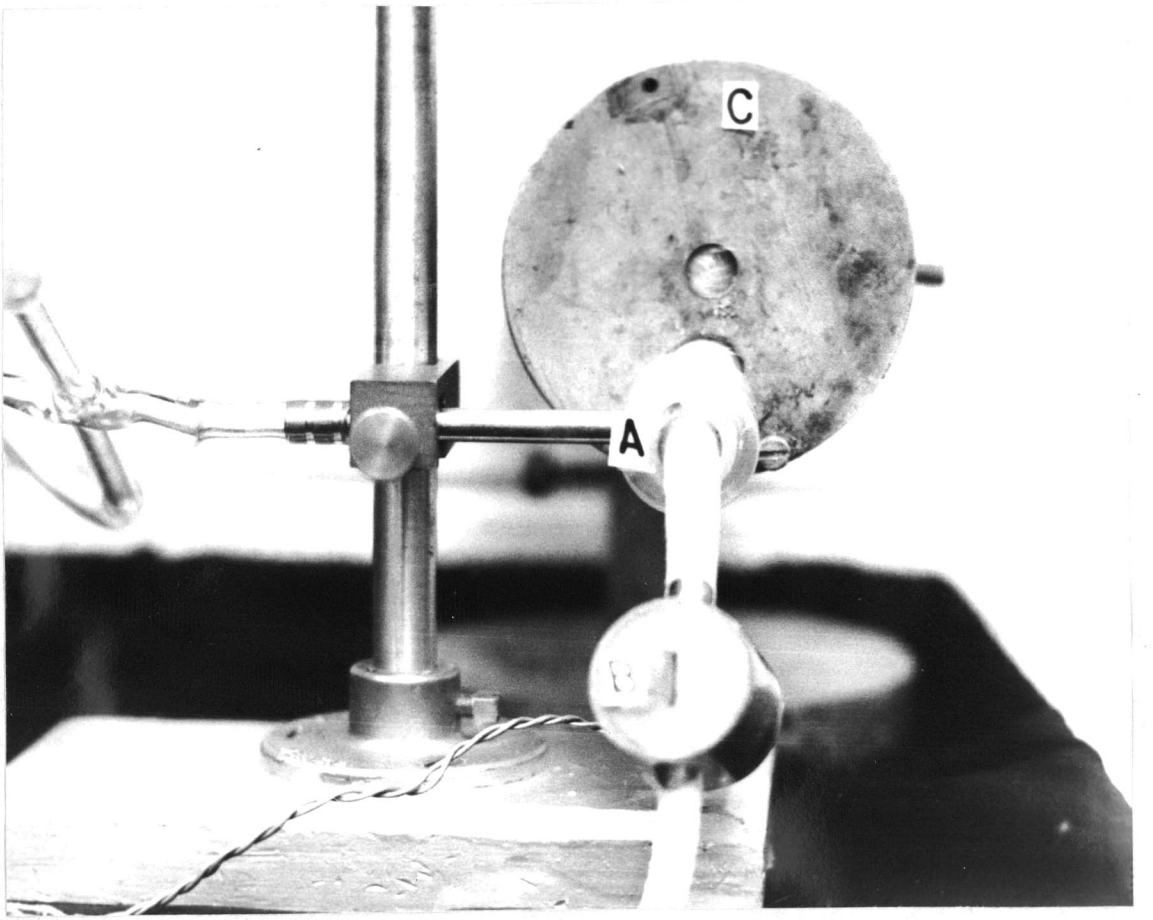

Fig. 1. A photograph showing the arrangement of the microphone and pneumatic cuff on the rats tail. The microphone is just behind the cuff, A. pneumatic cuff, B. microphone, and C. animal holder.

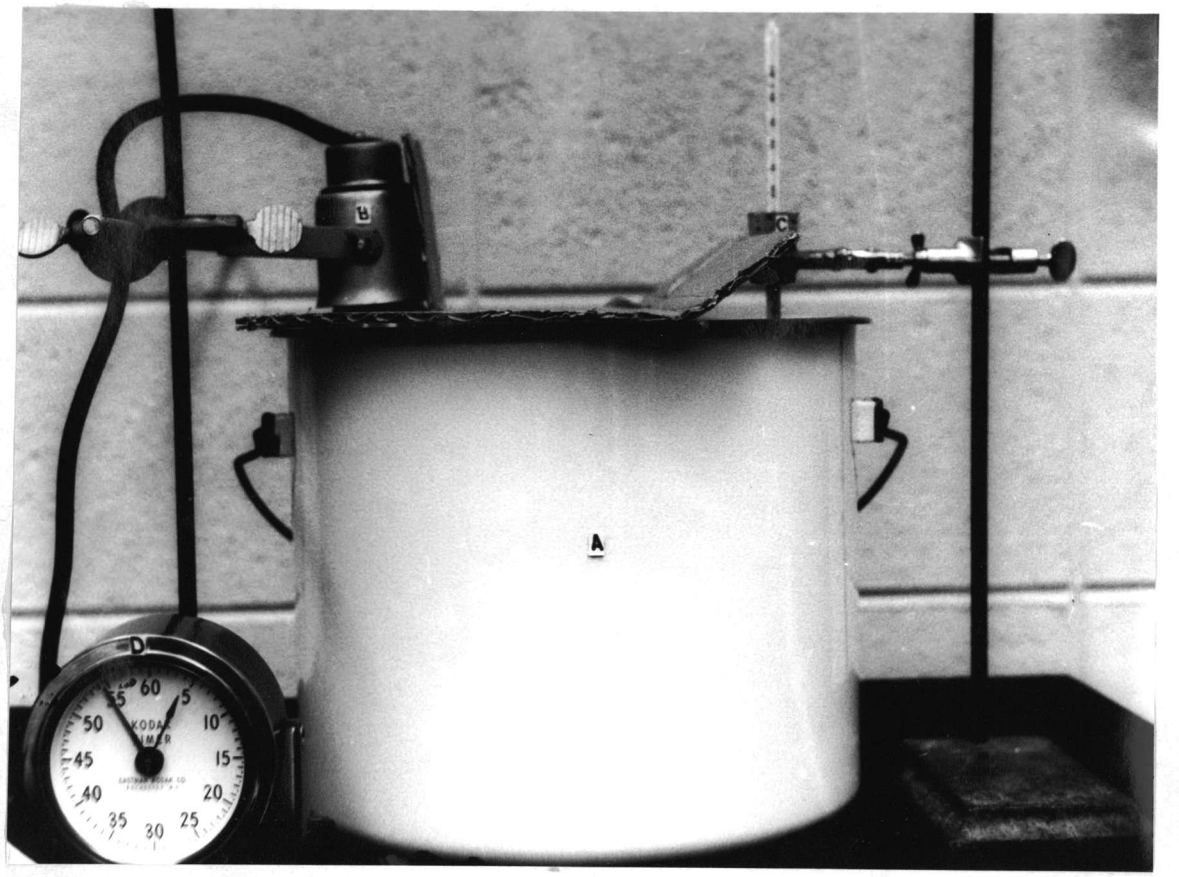

Fig. 2. A photograph of the warming chamber used which preceded the blood pressure measurements.

Group A consisted of 8 animals with the right kidney removed and the left renal artery partially obstructed. Group B consisted of 8 animals with the right kidney removed and the left kidney intact. Group C consisted of 6 control animals with both kidneys intact.

Goldblatt (1940) showed that when blood flow to a kidney of the dog was considerably reduced (ischemic kidney) by a clamp on the renal artery, hypertension ensued which persisted for several weeks and slowly subsided. The condition was relieved by removal of the clamp or of the ischemic kidney. The condition was made more severe when both kidneys were made ischemic, or one was made ischemic and the other removed.

Instead of using a Goldblatt clamp, the animals in group B were anesthetized with Nembutal (40 mg./kg. of body wt.) and black silk sutures (#000) were placed around the renal artery. Before tightening the loops in the sutures, a piece of chromel wire (.48 mm. diameter) was placed within the loop or slip knot. The suture thread was then tightened around the artery with the inserted wire until blood flow to the kidney ceased. The suture thread was again looped and tied and the wire removed immediately (Fig. 3). Partial obstruction in the renal artery was produced by placing the wire within the loop and the removal of it after tying the suture thread. The right kidney was then removed after this procedure was completed.

All operations were done under aseptic conditions. Although the kidneys are located retroperitoneally, an incision along the linea alba was the mode of entry into the peritonial cavity to expose the kidneys as seen in Figure 4. Care was taken not to obstruct nor damage the left ureter. The right adrenal gland was not removed in the animals of both operative groups (A and B).

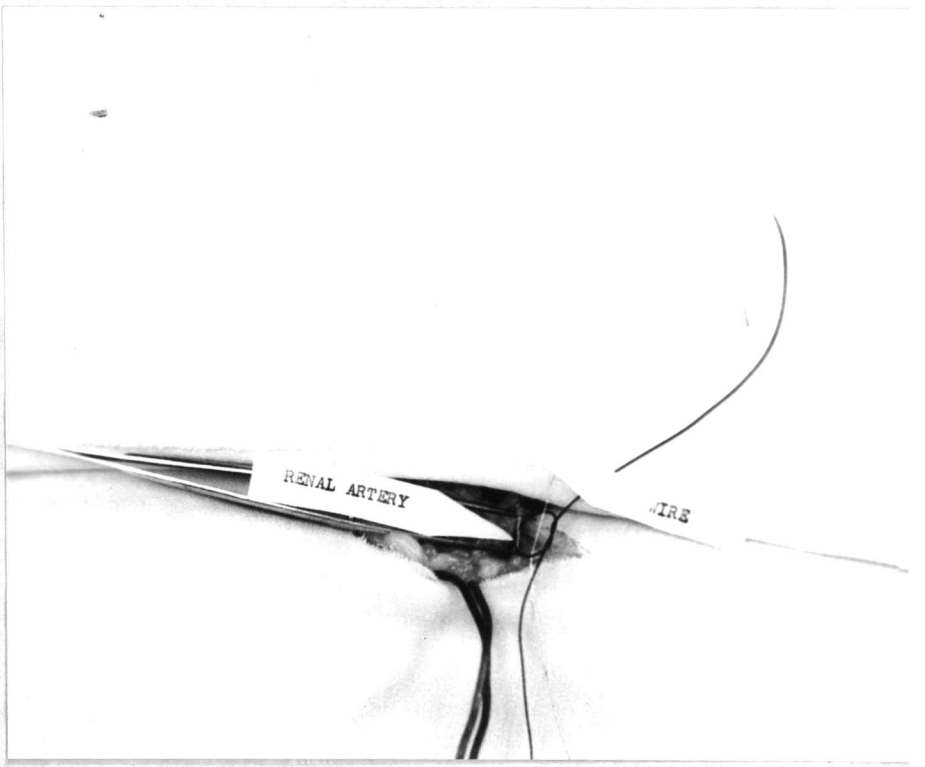

Fig. 3. A photograph which illustrates the positions of the wire, suture thread (black) and renal artery (stretched by forceps) before the small artery was partially ligated.

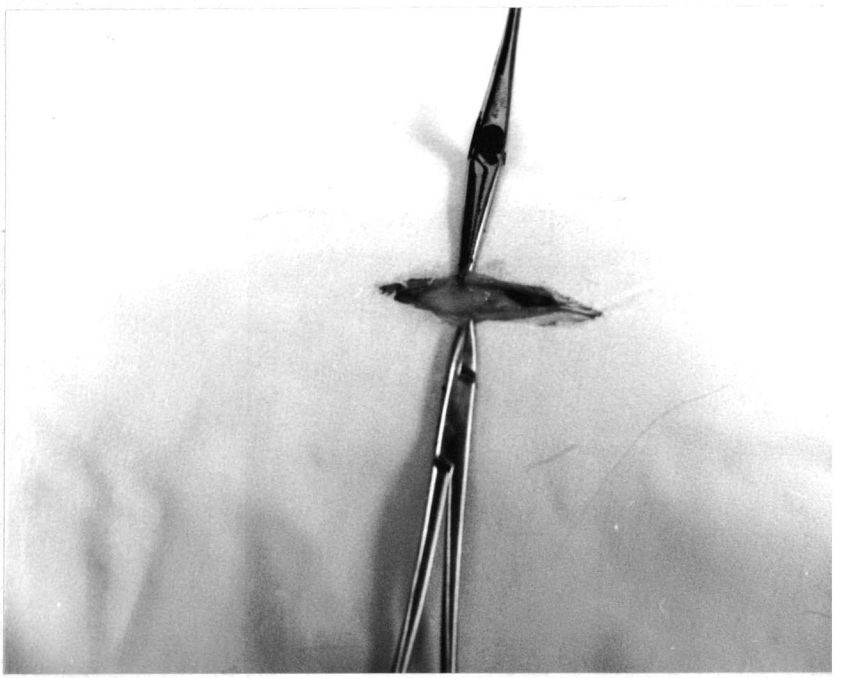

Fig. 4. A photograph showing the opening made mid-ventrally along the abdominal cavity. Hemostats are shown separating the skin and musculature along the linea alba.

Kidney function tests were done on all three groups. Inulin excretion determinations were performed according to the method used by Rolf, Surtshin and White (1949). Standard solutions were prepared as suggested by this method in order to establish a straight line for the computation of concentrations in the urine. Ten micrograms to 60 µg. in 2 ml. of distilled water constituted the range of the standard solutions.

Diphenylamine reagent was prepared by dissolving 2.5 gm. in 100 ml. of glacial acetic acid and 60 ml. of concentrated HCl. A 1:10 urine filtrate dilution was prepared and 2 ml. of this dilute solution was added to 4 ml. of the reagent. A blank was prepared for each set of determinations and 2 ml. of distilled water was used as the standard. The blank and samples were heated for 60 min. at 75°C and cooled in an ice bath for 2 min. before colorimetric determinations were done. As shown in Figure 5, urine was collected over a period of 24 hrs., using separate cages made especially for that purpose.

Phenolsulfonepthalein (Phenol Red) retention determinations were done according to the method used by D'Amour and Blood (1959).

Each test was done after it was established that the systolic blood pressure of the rats in Group A had developed renal hypertension. Groups A and B were compared with the controls (Group C).

Each animal in the three groups was anesthetized with Nembutal (40 mg./kg. of body wt.). An incision was then made through the femoral musculature to expose the femoral artery and vein (Fig. 6). A concentration of 5 mg./kg. body weight of phenol red was injected into the right femoral vein using a 2 ml. Luer-Loc syringe and a 27 gauge needle. Exactly 2 min. after the injection of the phenol red, 0.5 ml. of blood was collected from

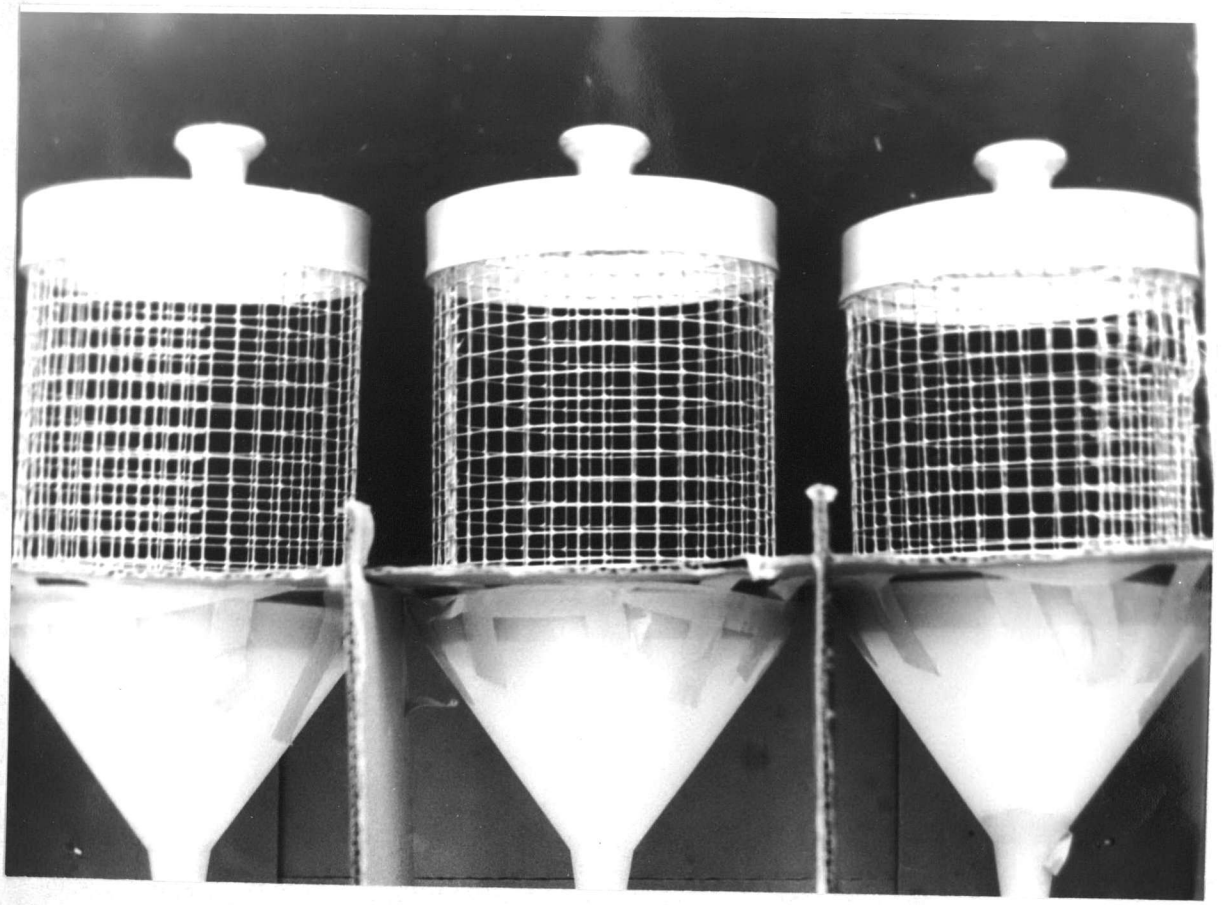

Fig. 5. A photograph showing the special cages used for the collection of urine.

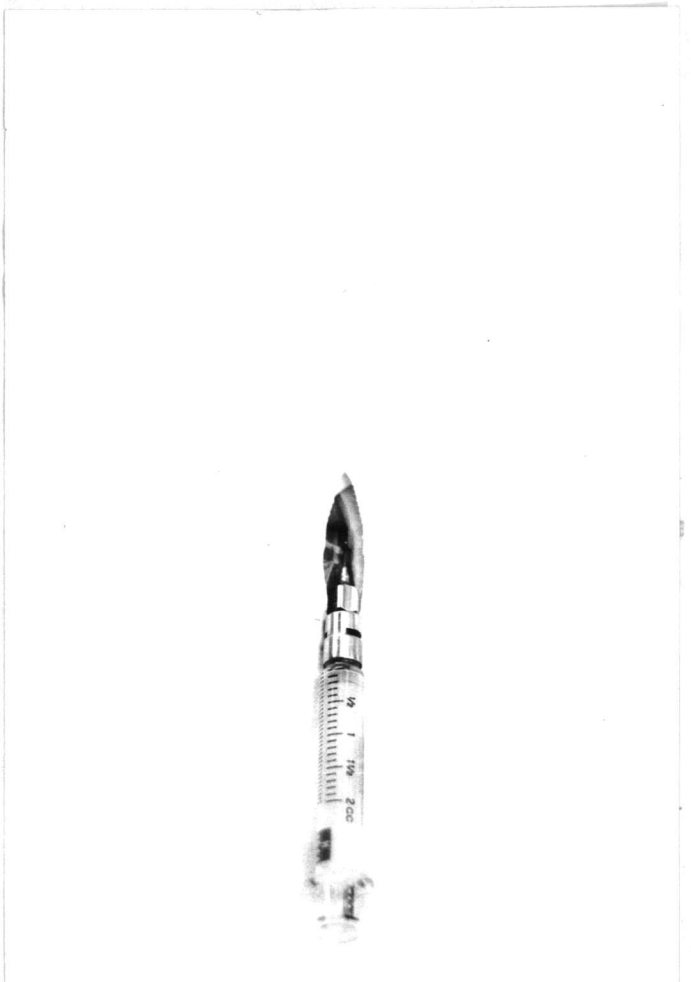

Fig. 6. A photograph illustrating the procedure used to intravenously inject phenol red and inulin.

the femoral artery and placed in a centrifuge tube for centrifugation. Preparation of standard solutions and colorimetric determinations were done, as stated previously, according to D'Amour and Blood.

After the kidney function tests were completed, the animals were weighed and sacrificed. The kidneys, heart and adrenals were removed for weighing to determine the per cent of body weight. These calculations were made by dividing each organ weight by the body weight of the animal and multiplying by 100. All organs removed were fixed in ten per cent formalin for at least 5 days to assure complete infiltration of the fixative into the tissues. The organs were weighed on a torsion balance with a sensitivity of $\pm$ .001 mg.

CHAPTER IV

EXPERIMENTAL RESULTS

During this investigation it was observed that the strain of rats used did not tolerate too well, the stress caused by the operations. It is suggested that a more sturdy strain be used for this type of investigation. Sprague-Dawley strain has been highly recommended by other investigators performing similar types of investigations.

The mean systolic blood pressure and body weight measurements were observed and recorded for three weeks prior to the operations. All of the animals showed normal growth patterns and appeared to be in good physical condition. Figure 7 illustrates the growth progress in terms of mean body weight and the mean systolic blood pressure characteristics are presented in Figure 8 during the three weeks before the operations were initiated.

All of the pertinent information involved in this phase of the investigation is included in Table 1.

Data concerning the differences found after the operations were performed are included in Table 2. It is important however, to emphasize at this point the observations concerning the body weight and systolic blood pressure measurements during the third week and those recorded after a 10-day recovery period. These are the mean values of Group A, B and C during the third week prior to operations; the body weights were 218 gms., 212 gms. and 221 gms., respectively. After the 10-day recovery period, Group A the mean body weight was 187 gms., Group B 226 gms. and Group C (controls) 238 grams.

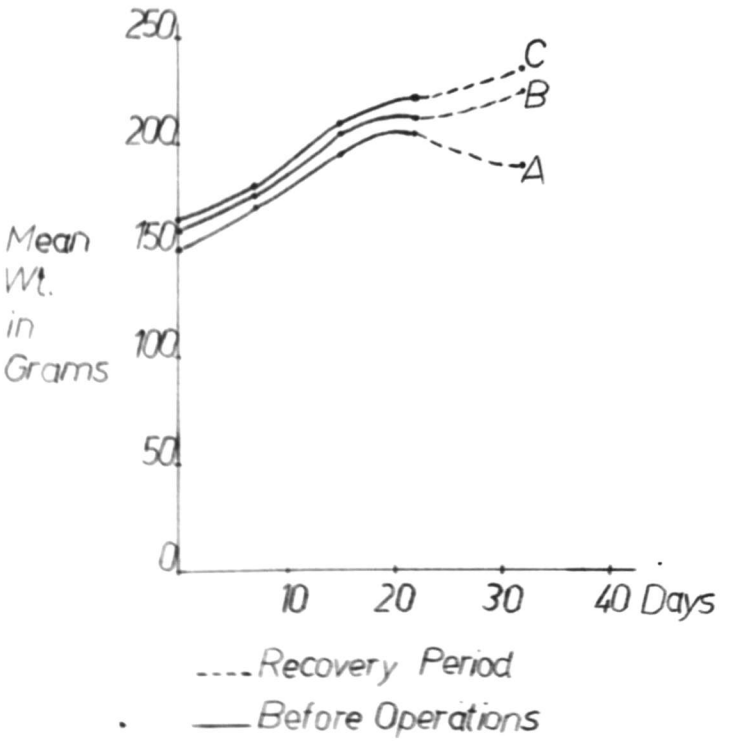

Fig. 7. A graph showing the mean body weight changes before and after operations.

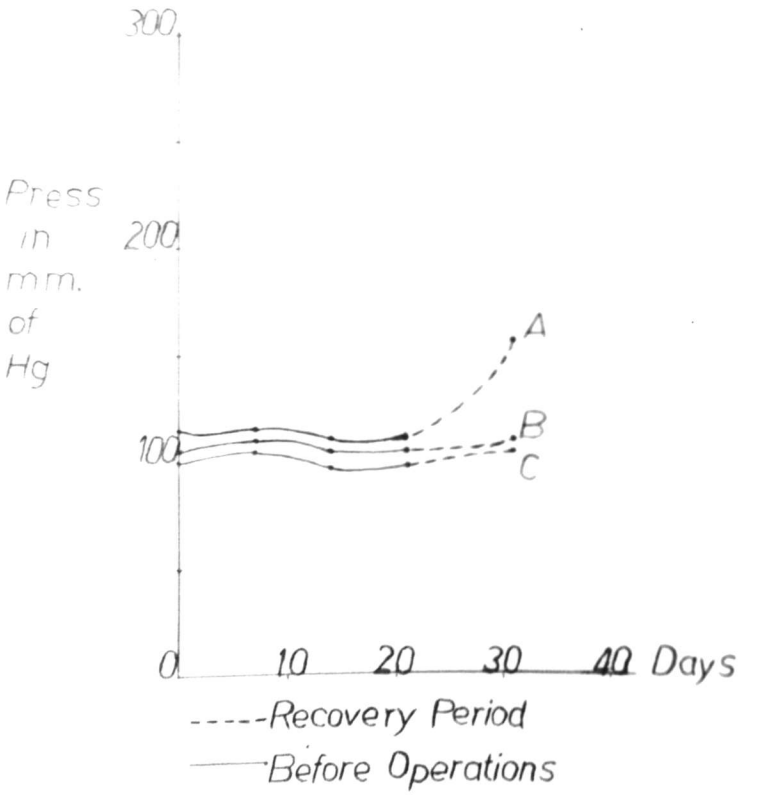

Fig. 8. A graph showing the mean systolic blood pressures before and after operations.

TABLE 1

A SUMMARY OF THE SYSTOLIC BLOOD PRESSURES AND BODY WEIGHTS
BEFORE OPERATIONS AND AFTER A 10-DAY RECOVERY PERIOD

	1st Week		2nd Week		3rd Week		10 days post op.	
Rat No.	Body wt.	Bl. Press.	Body wt.	Bl. Press.	Body wt.	Bl. Press.	Body wt.	Bl. Press.
A_1	163	107	180	111	206	121	162	152
A_2	162	102	185	80	219	109	176	160
A_3	167	121	195	111	215	106	205	176
A_4	182	122	196	117	213	119	187	149
A_5	195	108	222	120	242	107	205	150
A_6	180	113	205	109	225	108	208	155
A_7	160	109	177	112	205	111	166	156
A_8	163	112	198	108	220	114	188	158
Mean	172	112	195	109	218	112	187	157
B_1	171	118	210	119	227	100	242	108
B_2	140	97	175	104	182	86	200	101
B_3	167	110	198	116	200	97	211	110
B_4	209	121	235	97	243	129	258	121
B_5	204	103	216	101	225	112	247	103
B_6	174	109	200	110	195	104	205	109
B_7	176	101	200	112	211	108	223	100
B_8	170	98	197	102	210	105	225	102
Mean	176	107	204	108	212	105	226	107

Continued on next page.

TABLE 1--Continued

	1st Week		2nd Week		3rd Week		10 days post op.	
Rat No.	Body wt.	Bl. Press.	Body wt.	Bl. Press.	Body wt.	Bl. Press.	Body wt.	Bl. Press.
C_1	175	112	205	116	226	120	249	105
C_1^2	150	98	180	107	195	104	206	104
C_2^3	170	110	202	120	212	115	233	101
C_3^4	205	115	230	90	240	102	250	110
C_4^5	209	118	229	102	239	110	258	96
C_5^6	170	92	205	96	216	111	232	92
Mean	180	107	209	105	221	110	238	101

TABLE 2

INULIN CLEARANCE MEASUREMENTS TO DETERMINE THE RATE OF GLOMERULAR FILTRATION

Plasma Inulin conc. mg. per cent	Urine Inulin conc. mg. per ml.	Urine flow per hour	Inulin Filtered ml./hr.	Glomerular Filtration rate ml./per hour
		Group A		
81.0	.79	.12	.0095	.012
88.0	.85	.12	.0102	.012
100.0	.92	.14	.0129	.013
94.0	.91	.13	.0118	.013
103.0	.94	.14	.0131	.013
104.0	.94	.14	.0131	.013
86.0	.84	.11	.0092	.010
94.0	.90	.13	.0117	.012
* 94.0	.88	.13	.0114	.012
		Group B		
121.0	.96	.12	.0115	.010
100.0	.90	.12	.0108	.011
106.0	.87	.12	.0105	.010
129.0	.98	.20	.0196	.015
124.0	.95	.17	.0161	.013
103.0	.92	.13	.0112	.011
112.0	.89	.14	.0125	.011
113.0	.91	.15	.0137	.010
*113.0	.92	.14	.0132	.011
		Group C		
125.0	.96	.17	.0163	.013
103.0	.91	.12	.0109	.010
117.0	.93	.16	.0149	.013
125.0	.97	.16	.0155	.012
129.0	.96	.18	.0172	.013
106.0	.89	.12	.0115	.010
*117.0	.94	.15	.0157	.012

* = Mean Value

The unilaterally nephrectomized-partially ligated rats (Group A) elicited a mean loss in weight of 31.0 grams, while Group B, with only the right kidney removed showed a gain of 14.0 gms. As was expected, Group C (controls) had the largest weight increase of 19.0 grams.

The mean systolic blood pressures of Group A had an increase of 45 mm. of Hg (112mm.-157mm.) from the third week to the end of the 10-day recovery period. Groups B and C remained within a normaltensive range during the same period.

Kidney function tests were done following the recovery period and the results are recorded in Tables 2 and 3. Included in Table 2 are the data collected for the inulin clearance test which was used ultimately to determine the rate of glomerular filtration in each animal.

The mean rate of glomerular filtration in Table 2 and the per cent retention of phenol red (Table 3) exhibited a general and comparative summary of renal activity in each group.

The following data listed below illustrates briefly the results obtained from these test:

Glomerular Filtration, ml./hr.	Phenol red per cent Retention
Group A - 0.012	22.0%
Group B - 0.011	13.0%
Group C - 0.012	9.9%

It was found that the glomerular filtration rate in Group A was equal to the controls and slightly above Group B. The phenol red retention in the same group more than doubled that of the controls and was moderately increased over Group B.

The mean urine flow values were approximately equal for each group and the inulin filtered per hour was calculated by multiplying the urine

TABLE 3

PER CENT BODY WEIGHT MEASUREMENTS OF THE LEFT KIDNEY, RIGHT KIDNEY, HEART AND ADRENAL GLANDS

Body wt.	Wt. of left kidney in gms.	Per cent of body wt.	Wt. of right kidney in gms.	Per cent of body wt.	Wt. of heart in gms.	Per cent of body wt.	Wt. of adrenals glands in gms.	Per cent of body wt.
169.0	1.253	0.74			1.085	0.64	0.100	0.058
170.0	1.285	0.76			1.002	0.64	0.070	0.041
200.0	1.385	0.69			1.200	0.60	0.100	0.050
197.0	1.316	0.66			1.182	0.60	0.090	0.045
210.0	1.572	0.75			1.275	0.61	0.110	0.052
212.0	1.420	0.67			1.253	0.59	0.100	0.047
170.0	1.300	0.77			1.095	0.69	0.090	0.053
188.0	1.320	0.70			1.100	0.58	0.100	0.053
*190.0	1.350	0.73			1.160	0.62	0.095	0.050
245.0	1.390	0.57			1.025	0.42	0.110	0.045
212.0	1.577	0.74			1.195	0.57	0.100	0.047
215.0	1.570	0.74			1.200	0.56	0.092	0.046
260.0	1.496	0.57			1.050	0.40	0.125	0.046
255.0	1.550	0.61			0.855	0.31	0.084	0.031
230.0	1.328	0.58			1.020	0.44	0.092	0.039
235.0	1.268	0.54			0.956	0.38	0.110	0.047
247.0	1.390	0.56			1.035	0.42	0.105	0.042
*250.0	1.470	0.62			1.050	0.44	0.102	0.043

Continued on next page.

TABLE 3--Continued

Body wt.	Wt. of left kidney in gms.	Per cent of body wt.	Wt. of right kidney in gms.	Per cent of body wt.	Wt. of heart in gms.	Per cent of body wt.	Wt. of adrenals glands in gms.	Per cent of body wt.
255.0	1.095	0.43	1.120	0.44	1.062	0.42	0.085	0.031
220.0	1.015	0.46	1.025	0.47	0.095	0.41	0.065	0.029
245.0	1.045	0.42	1.075	0.43	1.055	0.42	0.080	0.032
265.0	1.126	0.42	1.115	0.42	1.120	0.42	0.092	0.034
269.0	1.172	0.43	1.095	0.40	1.128	0.42	0.091	0.033
250.0	1.087	0.43	1.117	0.44	1.029	0.40	0.082	0.032
*250.0	1.090	0.45	1.090	0.45	1.060	0.41	0.083	0.032

* = Mean Value

flow per hour by the concentration of inulin found in the urine.

The following formulae were used to calculate the glomerular filtration rate and inulin filtered in mg./hr.

$I_f = UxV$, where I_f equals inulin filtered in mg./hr., V, urine flow in ml./hr., and U, denotes the urine inulin concentration in mg. per ml.

$G = \frac{UV}{P}$ in which G is the glomerular filtration rate in ml. per hr., P, the plasma inulin concentration in mg. per cent.

$PSP = \frac{Pa}{Pv} \times 100$, in which PSP denotes phenolsulfophthalein, Pa, arterial plasma concentration of PSP in mg. and Pv, venous plasma concentration in mg. of PSP after 2 min. circulation time.

Figure 9 illustrates the relative values obtained for each kidney function test on a comparative basis.

Comparative studies of the per cent body weight of the left kidney (Group A), right kidney (Group B) and both kidneys (Group C) demonstrated a definite hypertrophy in rats Groups A and B. Heart and adrenal glands were also compared and the results indicated a definite increased per cent body weight when compared with controls.

The data for per cent body weight measurements are listed in Table 3. From an analysis of Table 3 one can readily observe that hypertrophy was a definite condition in both A and B groups. Included in Figure 10 are representative organs mentioned in this part of the investigation which illustrate the relative increases in size of organs from hypertensive and unilaterally nephrectomized animals along with the controls.

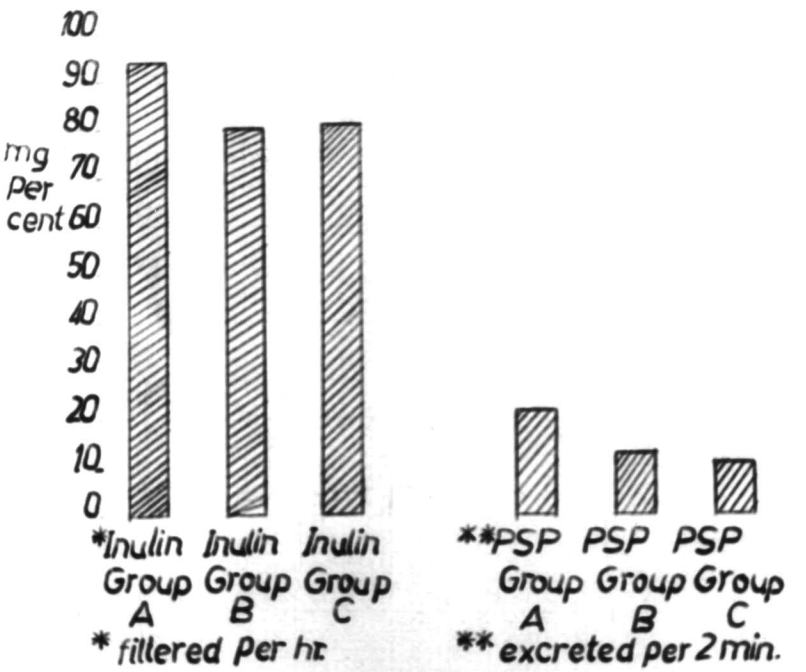

Fig. 9. A graph showing the relative filtration rate in ml. per hr. and phenol red retention in mg. per cent.

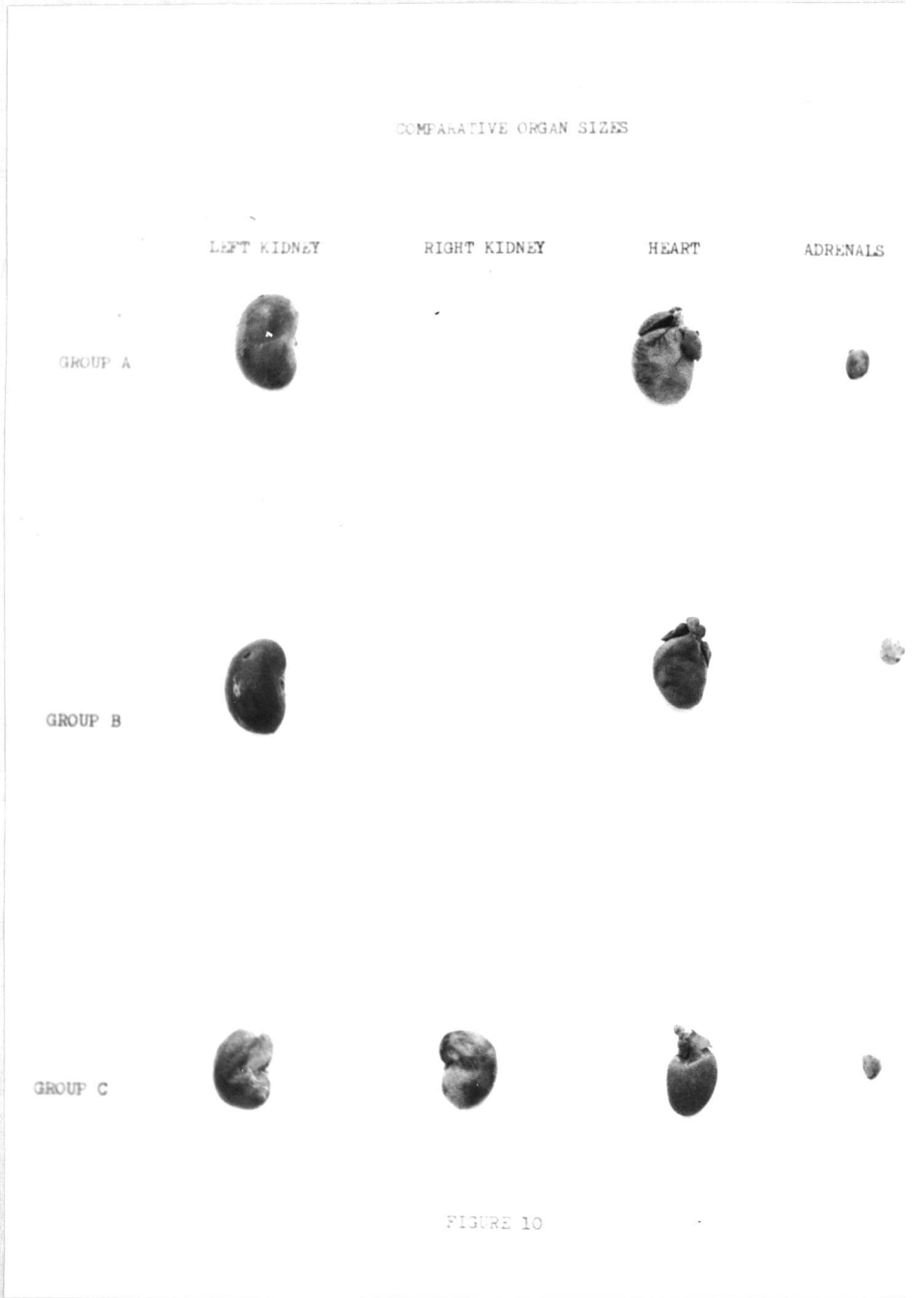

Fig. 10. A photograph showing the comparative sizes of representative organs of Group A, B and C.

CHAPTER V

DISCUSSION

This investigation confirmed Goldblatt's (1940) findings in relation to an elevated systolic blood pressure when decreased blood flow to the kidney was established. Although the technique for constricting the renal artery was different, the end result was similar. He also mentioned that upon release of the constriction, the kidney returns to a normaltensive condition and if one kidney is removed and the renal artery of the other remains constricted, a condition of chronic renal hypertension continued. In this report chronic renal hypertension was the condition studied, since the partial constriction sutures was not removed.

D'Amour and Blood, as previously stated, found that the mean systolic blood pressure of normal rats, weighing 100-175 grams, had an average systolic pressure of 103 mm. of Hg and ranged from 78 mm. to 132 mm. of Hg. Their results also included data from studies of renal hypertensive animals. Systolic blood pressures in these rats had a mean blood pressure of 175 mm. of Hg and ranged from 153 to 188 mm. of Hg. In this report it was found that the mean systolic blood pressure was 105 mm., and ranged from 90 mm. to 120 mm. in normaltensive rats and a mean of 157 mm. of Hg in hypertensive rats which ranged from 150 mm. to 176 mm. of Hg. Although two different types of detecting devices were used, plethysmographic (D'Amour and Blood) and microphonic, the values obtained were in close agreement.

Since it has been established that a decreased volume of blood flowing through the kidneys will produce ischemia and renal hypertension, what are some of the mechanisms involved and how do they compare with normal renal function?

Drury, et al. (1950) concluded that renal hypertension was produced by some substance formed by the kidneys and that this substance had a non-pressor function. Gordon and Flasher (1950) studied the effects of a non-pressor substance renin and that renal hypertension was mediated by a renin-angiotonin mechanism. Goldblatt (1940) had a similar view. However, Flasher and Drury (1950) did not support the contention that renin is the substance concerned in maintaining an elevated blood pressure in rabbits with early experimental hypertension. Friedman, Sugarman and Selzer (1941) found that renal ischemia was not necessary for the maintenance of chronic renal hypertension.

This investigation was not designed to evaluate the substance or substances which caused renal hypertension; instead, the chief purpose was to compare the physiological functions of a hypertensive system with a normaltensive one. It was found that hypertensive animals equalled or slightly exceeded the renal output of normaltensive and unilaterally nephrectomized ones. Retention of phenol red (PSP) which is easily bound by plasma proteins and readily excreted, was increased when compared with the controls. Loss of body weight during the chronic hypertensive state was evident. Increased per cent body weight of the remaining kidney, heart and adrenal glands elicited a definite hypertrophic condition in the experimental groups.

Concomitantly, the factors or results mentioned above may suggest that renal hypertension involves a close association of several systems acting together to suppress or resist a variation of the basal regulatory and excretory processes performed by the kidneys. Immediate reactions by the kidneys may be considered as a stress resisting phenomenon or an attempt to counteract immediate changes of a steady state system.

Results found in each of the experimental animals demonstrated that the heart, adrenals and the remaining kidney had some evidence of hyperactivity. Increased glomerular filtration was thought to be associated with an increase in cardiac output by means of an elevated systolic blood pressure. Increased phenol red retention or decreased excretion was associated with an attempt by the tubules of the kidney to maintain a plasma threshold concentration by the process of reabsorption. This also may be associated with the colligative properties of the plasma proteins.

Adrenal activity was evident, based on hypertrophy only, which may suggest a hormonal influence. If the adrenals were hyperactive in the experimental animals, it seems as though it would be safe to assume that the pituitary was also active, as stated by Brown and Barker (1962), although this investigation did not involve a study of the pituitary gland.

If all of these systems were working simultaneously, which seemed to have been evident, it is difficult to understand how one enzyme or enzymatic reaction can be the single cause of renal hypertension.

CHAPTER VI

SUMMARY AND CONCLUSION

The foregoing study involved the investigation of renal function in hypertensive and normaltensive female albino rats. It was found that the systolic blood pressure was elevated, glomerular filtration was increased, phenol red retention increased, and hypertrophy of the kidneys, hearts and adrenal glands of experimental animals occurred.

The hypertensive animals elicited an ability to perform basal regulatory and excretory functions while under conditions of stress. Stress was indicated by a loss of weight and a failure to gain weight when compared with unilaterally nephrectomized and control animals.

The following conclusions were made based on the results obtained:

1. Partial constriction of the renal artery to one kidney and removal of the other kidneys will result in the production of an elevated systolic blood pressure in the rat.

2. Inulin clearance studies, indicated an increase in glomerular filtration based upon an increase in the hydrostatic pressure produced by the heart.

3. The excretion of vital plasma minerals was reduced to maintain a critical plasma concentration of the same.

4. Hypertrophy of the remaining kidneys, heart and adrenal glands was indicative of interrelated systems reacting to maintain homeostatic conditions.

5. It is doubtful that a reaction by a single chemical will cause renal hypertension. Increased renin concentrations may be only part of a complex feed-back mechanism which is dependent upon others in order to maintain a steady state within the organism.

6. Renal hypertension may be thought of as a compensatory mechanism to resist a condition of stress until the body can readjust to the changed conditions, or until the stress conditions subside.

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